Diethylstilbestrol

CAS #56-53-1
Swiss CD-1 mice, at 0.0, 1.0, 10.0, and 50.0 PPB in feed
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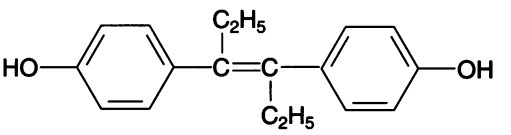
Started 6/16/82; Completed 12/18/84
NTIS #PB85167674/AS



Diethylstilbestrol (DES), the least expensive and most widely used estrogen, was tested in Swiss CD-1 mice using the RACB protocol (Lamb et al., J Am Coll Toxicol 4(2):173–184 [1985]). This study was one of the first RACB studies conducted. DES was chosen as a known positive, based on the extensive literature by MacLachlan and colleagues. There were two laboratories beginning to run RACB studies, and a DES study was performed at each of these laboratories to address the issue of interlaboratory variability. From the dose-range-finding study (Task 1), levels of 1.0, 10.0 and 50.0 ppb in feed were selected for the continuous breeding phase of the study. Based on body weights and measures of food consumption, the estimated average doses were approximately 0.15, 1.5, and 7.70 µgm/kg/day.

In Task 2, no adverse clinical signs were noted; one high dose female died of partner-inflicted wounds. Body weight was unaffected during Task 2. The mean number of litters per pair was reduced to approximately 30% of control at the high dose, while the number of live pups per litter was reduced by 77 and 64% in the medium and high dose groups, respectively. Adjusted live pup weight was unaffected. The high dose group took longer to deliver each of the first three litters; no fourth or fifth litters were delivered at 50 ppb.

Since adverse effects were noted in Task 2, Task 3 was conducted using the using the control and high dose mice. Compared to controls, only one-third as many exposed female mice delivered a litter, and these litters contained approximately 60% fewer pups. Interestingly, for the exposed female group, adjusted pup weight was reduced by approximately 20%. The only adverse effect noted in the group containing exposed males was a 10% reduction in adjusted pup body weight. The larger adverse effects were clearly seen in exposed females.

After the Task 3 litters were evaluated, the F_0 control and high dose mice were killed and necropsied. For females, the only effect noted was an approximately 30% increase in pituitary weight. For females, 25% of controls had an unclear estrous cycle, while greater than 75% of treated females did not have a clear estrous cycle. In males, a significant increase in pituitary weight (approximately 15%) was also seen, along with 13 to 18% reductions in the weight of epididymis, cauda epididymis, and prostate. There were no demonstrable sperm effects.

Task 4, the F_2 generation assessment, was not conducted.

This study replicated all of the salient features of the other diethylstilbestrol study: female as the much more sensitive gender in the absence of significant weight effects. Differences between the results of the two studies include effects in the middle dose group, different responses in adjusted pup weight (increased at one lab, decreased at the other), and an effect on pup number in the middle dose in Task 2 (unchanged at one lab, reduced by 11% at the other). Nonetheless, in broad strokes, these studies confirmed the general replicability of the data from two different laboratories, and provided a sense of the degree of variation that might be expected across labs.

Summary: NTP Reproductive Assessment by Continuous Breeding Study.

NTIS#: **PB85167674/AS**
Chemical: **Diethylstilbestrol**
CAS#: **56-53-1**
Mode of exposure: **Feed**
Species/strain: **Swiss CD-1 mice**

F_0 generation Dose concentration →	1 PPB	10 PPB	50 PPB
General toxicity	Male, female	Male, female	Male, female
Body weight	—, —	—, —	—, —
Kidney weight[a]	•, •	•, •	•, •
Liver weight[a]	•, •	•, •	—, —
Mortality	—, —	—, —	—, —
Feed consumption	—, —	—, —	—, —
Water consumption	•, •	•, •	•, •
Clinical signs	—, —	—, —	—, —
Reproductive toxicity			
x̄ litters/pair	—	—	↓
# live pups/litter; pup wt./litter	—, —	↓, —	↓, —
Cumulative days to litter	—	—	↑
Absolute testis, epididymis weight[a]	•, •	•, •	—, ↓
Sex accessory gland weight[a] (prostate, seminal vesicle)	•, •	•, •	↓, —
Epidid. sperm parameters (#, motility, morphology)	•, •, •	•, •, •	—, —, —
Estrous cycle length	•	•	—
Determination of affected sex (crossover)	Male	Female	Both
Dose level	—	50 PPB	—
F_1 generation Dose concentration →			
General toxicity	Male, female	Male, female	Male, female
Pup growth to weaning	•, •	•, •	•, •
Mortality	•, •	•, •	•, •
Adult body weight	•, •	•, •	•, •
Kidney weight[a]	•, •	•, •	•, •
Liver weight[a]	•, •	•, •	•, •
Feed consumption	•, •	•, •	•, •
Water consumption	•, •	•, •	•, •
Clinical signs	•, •	•, •	•, •
Reproductive toxicity			
Fertility index	•	•	•
# live pups/litter; pup wt./litter	•, •	•, •	•, •
Absolute testis, epididymis weight[a]	•, •	•, •	•, •
Sex accessory gland weight[a] (prostate, seminal vesicle)	•, •	•, •	•, •
Epidid. sperm parameters (#, motility, morphology)	•, •, •	•, •, •	•, •, •
Estrous cycle length	•	•	•

Summary information	
Affected sex?	Female
Study confounders:	No second generations
NOAEL reproductive toxicity:	1 ppb
NOAEL general toxicity:	10 ppb
F_1 more sensitive than F_0?	Unknown
Postnatal toxicity:	Unknown

Legend: —, no change; •, no observation; ↑ or ↓, statistically significant change ($p<0.05$); —, —, no change in males or females. [a]Adjusted for body weight.